IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

ARIEL G. NOTCOVICH et al		Art Unit:	1641
Application No.:	10/578,860	Examiner:	LAM, ANN Y
Filed:	June 30, 2006	Docket No.:	27396U

For: SYSTEM AND METHOD FOR CARRYING OUT MULTIPLE BINDING REACTIONS IN AN ARRAY FORMAT

DECLARATION UNDER 37 C.F.R. §1.131

I, Dr. Tsafrir Bravman, a citizen of Israel, residing at Nesher, hereby declare and state:

1. I have a Ph.D. degree in Biotechnology & Food Engineering from the Technion, Israel Institute of Technology. I have over 6 years of experience in development of applications for biosensor systems and chips.

2. I am the Chief Executive Officer of Bio-Rad, Haifa, Israel.

3. I am currently employed by Bio-Rad Haifa (formerly ProteOptics) and have been continuously employed by the same since 2004. I am an executive member of the team that developed the presently claimed subject matter, i.e., the subject matter of ProteOn XPR36 system and chips being the subject of the present invention.

4. I have published the following articles related to the ProteOn system or chips:

- V. Bronner, G. Denkberg, M. Peled, Y. Elbaz ,E. Zahavi, H. Kasoto, A. Notcovich and T. Bravman: Therapeutic Antibodies Discovery and Development Using the ProteOn XPR36 Biosensor Interaction Array System. *Anal. Biochem.* 2010;
- Nahshol, V. Bronner, A. Notcovich, L. Rubrecht, D. Laune and T. Bravman: Parallel Kinetic Analysis and Affinity Determination of Hundreds of Monoclonal Antibodies Using the ProteOn XPR36. *Anal. Biochem.* 2008;

T.B.

- V. Bronner, T. Bravman, O. Nahshol: Evaluating Candidate Lead Compounds by Rapid Analysis of Drug Interactions with Human Serum Albumin. *American Biotechnology Laboratory* 2008;

- T. Bravman, V. Bronner, O. Nahshol, Gideon Schreiber: The ProteOn XPR36™ Array System – High Throughput Kinetic Binding Analysis of Biomolecular Interactions. *Cellular and Molecular Bioengineering* 2008; and

- T. Bravman, V. Bronner, K. Lavie, A. Notcovich, G.A. Papalia, D.G. Myszka: Exploring "one-shot" kinetics and small molecule analysis using the ProteOn XPR36 array biosensor. *Anal. Biochem* 2006.

5. The following facts demonstrate conception of the invention, coupled with due diligence to a subsequent reduction to practice, of the presently claimed subject matter in ISRAEL, on a date prior to the Third day of March in the year TWO-THOUSAND AND THREE (03/03/2003), which date is, upon information and belief, the earliest possible effective filing date of US Patent Application Publication No. 20060210984 ("the Lambert reference"), cited by the Examiner in the Official Action dated March 24, 2010.

6. It is noted that the Lambert reference is a national phase entry of International Patent Application No. PCT/US04/06479, which claims priority to US Provisional Patent Application No. 60/451,468. US Provisional Patent Application No. 60/451,468 was filed on March 3, 2003. Applicants note that while March 3, 2003 is the earliest possible effective filing date for the Lambert reference as prior art under 35 USC §§ 102 and 103, this declaration is not an admission that the Lambert reference is actually a valid reference as of March 3, 2003 for at least the reason that the disclosure relied upon by the Examiner in the Lambert reference may not be fully supported by the March 3, 2003 filing date. However, as shown herein below, since invention of the presently claimed subject matter occurred prior to March 3, 2003, it is submitted that the Lambert reference is not prior art against the presently claimed subject matter within the meaning of 35 USC §§ 102 and 103.

T. B.

7. The present application describes, for the first time, a system and method for determination of kinetic parameters of a binding reaction, referred to herein as "*One-Shot Kinetics*" (OSK) which was implemented in the "*ProteOn*" instrument. "*ProteOn-E*" is a developmental stage technology of the One-Shot Kinetics technology described in the present application.

8. The One-Shot Kinetics provides a solution to the lack of high throughput technology which enables real-time, label-free monitoring of kinetics of multiple bio-molecular interactions involving a plurality of analyte concentration combinations, all at the same "shot."

9. It is submitted that conception and reduction to practice of the presently claimed *ProteOn* technology was made as early as **June 14, 2002**. As evidence of this, Applicants provide herewith Annexes A-C, which are discussed in paragraphs 10-19 below.

10. Annex A, submitted herewith as a part of this declaration, is a copy of an electronic document that describes ProteOn microfluidics technology. Annex A describes the ProteOn microfluidics as presently claimed. As shown on page 1 of Annex A, i.e., the 'File Properties' page, Annex A was created on **June 14, 2002**.

11. Pages 2-4 of Annex A, i.e., page 1-3 of the document entitled "ProteOptics Micorfluidics Specification," describe a microfluidic system for monitoring protein-protein interactions in which a set of proteins are immobilized on an assay chip. The microfluidic system was designed to have a crisscross configuration (this phrase was sometime interchangeably used with "*XrissXross*") to enable immobilization and thereafter monitor and/or measure their plurality of binding reactions. The system, at the time, had a configuration permitting 8x8 binding reactions; however, the claimed subject matter is not limited to a specific number of such *XrissXross* channels.

T.B.

12. As described in Annex A, a minute amount of buffer and sample can be simultaneously delivered to a surface of an assay chip. As shown on the third page of Annex A, i.e., page 2/3 of the document entitled "ProteOptics Micorfluidics Specification," at item (h), the system was configured to handle or work on all channels, simultaneously. This feature was introduced to considerably reduce stabilization time.

13. It is respectfully noted that Annex A was not only aimed at addressing general features, but also to address the size of different components of the microfluidic system. Channel dimension were further addressed together with, for example, the required spacing between the channels and cover size. The technical features of the actively controlled valves were presented. Furthermore, automatic connection of the piping including connection to input and output ports was addressed. As shown, the controlled valve system was designed and the monitoring zone for the protein-protein interactions was determined.

14. Annex B is a document summarizing the details of a technological meeting held on **September 24, 2002** to discuss the presently claimed subject matter. As stated, the experienced proteomics engineering group was involved in the developmental meeting. As provided in the document, the *XrissXross* prototype was discussed, including various strategies material to the technology. The meeting addressed different prototypes and subsystems to be included. In addition, preparation of the testing phase was also discussed and designed during the meeting.

15. The Bio-Rad Board of Directors received an updated report regarding the *ProteOn* project. The summary detailing the report dated **February 2, 2003** is attached as Annex C. Annex C is an internal document distributed at Bio-Rad, the assignee of the present application. The achievements in various aspects of the *ProteOn* project were noted in the report. Emphasis on the 2003 budget and other financial issues were raised as issues to be considered. *ProteOn* system was reported to work appropriately and stability experiments were reported as being in progress. Buffer flow and sample injections were reported as being in a testing phase.

T.K.

16. As Annexes A-C demonstrate, the inventors conceived and continually reduced the invention to practice until the actual date of filing of the earliest possible effective filing date of the Lambert publication, i.e., prior to March 3, 2003. At no point along the way did the inventors or the applicant abandon the invention.

17. The work reported in each of Annexes A-C was performed in ISRAEL. In addition, the invention was reduced to practice in ISRAEL.

18. In view of the evidence in Annexes A-C it is submitted that the invention of the presently claimed subject matter, within the meaning of 37 CFR § 1.131, occurred prior to the Third day of March in the year TWO-THOUSAND AND THREE (03/03/2003), which date is, upon information and belief, earliest possible effective filing date of the Lambert publication.

19. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and/or imprisonment under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Date: 19/9/2010

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